

Point of Care Prothrombin Time/International Normalized Ratio Devices for Monitoring Warfarin Therapy

SCOPE

The FDA has become aware of performance problems associated with point of care (POC) Prothrombin Time (PT)/International Normalized Ratio (INR) devices that raise patient safety concerns. Numerous reports of serious adverse events for POC PT/INR devices have been submitted to the FDA. The FDA's postmarket analysis of these reports indicates that the adverse events appear to be linked to inaccurate performance of POC PT/INR devices in both home-use (self-testing) and professional healthcare settings. The accuracy, reliability, result reporting, and device usability of the PT/INR devices appear to have led to erroneous patient INR results. Therefore, the FDA is addressing the scientific and regulatory challenges associated with POC PT/INR devices' safety and effectiveness in a public workshop at the White Oak Campus, Silver Spring, Maryland on January 25, 2016.

The FDA is presenting this discussion paper to guide workshop attendees as part of the preparation for the workshop. FDA would like to obtain feedback on how to address the challenges related to design, development, and evaluation of POC PT/INR medical devices for both prescription use under appropriate professional supervision and home use. Interested parties may submit written comments to Docket No. FDA-2015-N-4462.

The information and questions contained in this document are not binding and do not create or propose new requirements or expectations for affected parties, nor is this document meant to convey FDA's proposed or recommended approaches or guidance.

GOAL

This discussion paper provides a brief overview of the regulatory challenges facing POC PT/INR devices for monitoring warfarin therapy and the regulatory strategies being considered to help improve device performance.

BACKGROUND

Warfarin works by blocking the formation of vitamin K–dependent clotting factors and is the most commonly prescribed oral anticoagulant drug in the United States. It is used to reduce the risk of serious thromboembolic events, such as strokes, caused by harmful blood clots. However, because warfarin reduces the ability of blood to clot, it also increases the risk of serious bleeding. To be used safely and effectively the anticoagulant effect of warfarin must be maintained in a range that balances the desired effect of prevention of thromboembolism with an increased risk of bleeding; i.e. the ability of the blood to clot must be sufficiently reduced to prevent harmful blood clots without causing excessive bleeding. A patient's response to warfarin can be significantly influenced by numerous factors such as other medications, diet,

and age, as well as genetic variation, particularly in the genes for CYP2C9 and VKORC1.¹ As a consequence, warfarin dosage must be individually tailored to maintain patients within the desirable anticoagulation range. If the dose of warfarin is too low, then the risk of major thromboembolic events, such as stroke, increases. If the dose is too high, then the risk of major bleeding unnecessarily increases. Therefore, periodic monitoring of a patient's level of anticoagulation in response to warfarin is required.

Warfarin monitoring can be accomplished by a plasma-based laboratory test or a whole blood point of care device, both of which report INR. The INR is calculated from the PT result, which is a measure of how long it takes blood to clot when thromboplastin is used to initiate the coagulation cascade. Due to the variability in PT results observed among laboratories from the use of different commercialized thromboplastin reagents, the INR calculation was established by (World Health Organization) WHO to standardize the clotting measurement.

Point of care testing (POCT)—testing patients' samples in a physician's office or at home instead of in a clinical laboratory — is a growing part of patient testing in general, as continuing improvements in technology have increased user preferences for testing with POC devices. POC PT/INR devices are frequently used in clinical practice for monitoring warfarin therapy, typically providing the end user with INR results. POC PT/INR devices offer a number of benefits for improved monitoring of warfarin therapy:

1. POC PT/INR devices require only a small volume of whole blood obtained by fingerstick. Most patients prefer fingerstick to more invasive venipuncture.
2. POC PT/INR devices eliminate potential problems related to specimen handling and transport.
3. POC PT/INR devices provide immediate results, which allow for rapid clinical decision making.
4. The portability of POC devices allows PT/INR testing in a variety of settings (physician offices, long-term facilities, home use, emergency departments, etc, which greatly facilitates patient monitoring.^{2,3}

The following sections will discuss regulatory requirements, various challenges the Agency is facing and identify areas that may require increased consideration in the regulatory review process for these devices.

FDA Approach for Substantial Equivalence Assessment of POC PT/INR Devices

FDA regulates POC PT/INR devices as Class II medical devices and requires sponsors to submit a 510(k) to FDA for premarket review and clearance. Class II medical devices generally carry

¹ <http://www.nature.com/tpj/journal/v7/n2/pdf/6500417a.pdf>

² Bluestein, et al. Measuring INR in Long-Term Care: A Comparison of Commercial Laboratory and Point-of-Care Device Results. JAMDA. 2007 Jul;8(6):404-8.

³ <http://www.clinchem.org/content/57/9/1219.full.pdf+html>

moderate risk that is mitigated by special controls, which, in combination with general controls regarding labeling, manufacturing, etc., are necessary to demonstrate that the new device is substantially equivalent to a device that already is legally marketed (predicate).⁴ A finding of substantial equivalence means that the Intended Use of the new device falls within the scope of the Intended Use of the predicate device, and the new device either has the same technological characteristics, or has different technological characteristics but (i) any differences in technological characteristics do not raise different questions of safety and effectiveness and (ii) information submitted demonstrates that the new device is as safe and effective as the predicate device.⁵

Current Requirements for Assessing Substantial Equivalence of POC PT/INR Devices

The following are performance studies that are carried out in establishing the analytical and clinical performance of POC PT/INR devices. The goal of these studies is to demonstrate that the marketed device meets necessary performance characteristics and that the manufacturer understands and communicates the limitations of the device.

- A. Analytical Performance
 - i. Precision
 - ii. Analytical Measurement Range or Reportable Range
 - iii. Analytical specificity
 - iv. Factor Sensitivity
 - v. Traceability
 - vi. Stability
 - vii. Quality control
 - viii. Cleaning and disinfection efficiency and instrument robustness
- B. Comparison Studies
 - i. Method comparison with predicate device and reference method
 - ii. Sample matrix comparison
- C. Reference Range

Upon clearance, the FDA categorizes POC PT/INR devices for use in professional settings (e.g., physician's offices) as CLIA moderate complexity devices. For prescription home use PT/INR devices, the FDA categorizes the devices as CLIA waived as determined by 42 U.S.C. 263a(d)(3).

CURRENT CHALLENGES IN THE EVALUATION OF SUBSTANTIAL EQUIVALENCE OF POC PT/INR IN VITRO DIAGNOSTIC MEDICAL DEVICES

POC PT/INR devices marketed today use several clot detection technologies (electrochemical, impedance, optical, etc.) which require customized analytical validation experiments. Complex,

⁴ Federal Food, Drug, and Cosmetic Act section 513(a)(1)(B) (21 U.S.C. 360c (a)(1)(B))

⁵ Federal Food, Drug, and Cosmetic Act section 513(i) (21 U.S.C. 360c(i)). For more information on how FDA evaluates 510(k)s, refer to the FDA guidance entitled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]."

technology-specific mathematical algorithms are used to determine the clotting end point to calculate PT and INR results. The inherent differences between various clot detecting technologies may affect the comparability between the INR results obtained from different PT/INR devices. For example, direct clot measuring devices measure the physical clot with a possibility of reduced interference from blood constituents not involved in clot formation. Conversely, devices that employ indirect clot measurements use a secondary means of clot detection (e.g., detecting changes in current across a sample), which may increase the possibility of interference from blood constituents and inflammatory molecules not involved in the clotting cascade. These interferents include patient medications (e.g., antibiotics⁶), patient specific sample differences (e.g., fibrinogen, platelet and hematocrit concentrations⁷) and certain disease conditions (e.g. antiphospholipid syndrome⁸). Technology-specific interference studies should be a part of the 510(k) submission for these devices. Therefore, technology specific interference studies should be considered as part of the 510(k) submission process for these devices.

A further challenge for evaluating POC PT/INR devices is the broad spectrum of patients for which the devices are intended to be used. POC PT/INR devices are utilized by patients with different physiological and pathological factors, such as non-ambulatory nursing home patients and patients utilizing an outpatient Coumadin clinic. Certain blood sample attributes, including drugs and blood constituents, could interfere with PT/INR measurements causing inaccurate results and therefore incorrect warfarin dosing. In addition, the wide variety of end-users for these POC devices requires extensive training and quality control elements in order to prevent inaccurate and imprecise test results from being generated.

Another potential challenge associated with POC PT/INR device testing is the difference between test sample matrices, that is, plasma versus whole blood. Conventional PT/INR laboratory tests use citrated plasma as the sample, whereas POC PT/INR devices typically use whole blood (which includes cellular and extracellular elements). To date, a requirement for a direct comparison between the two matrices, using the lab-based assay as the reference method, has been required for device clearance. However, the clotting differences between whole blood and plasma can be profound and require careful evaluation. For some clinical conditions, obtaining a fingerstick sample and collecting an adequate amount of venous blood can be challenging. For instance, if the site of sample collection (finger) is cold or the patient has a condition affecting finger temperature (e.g. peripheral vascular disease), specimen collection may be hindered². Additionally the two sample matrices have different components, as mentioned above, and are not always directly comparable. For example, tissue activating factor released from fingersticks is another factor that can alter the accuracy of POC PT/INR devices⁹. Because some subjects may not bleed as freely as others, an insufficient amount of

⁶ Pottegård, A., et al. Change in International Normalized Ratio Among Patients Treated with Dicloxacillin and Vitamin K Antagonists. *JAMA*. 2015; 314(3): 296-297.

⁷ <http://ajcp.ascpjournals.org/content/133/4/550.full.pdf+html>

⁸ <http://aop.sagepub.com/content/48/11/1479.full.pdf+html>

⁹ Finck KM, et al. Clinical impact of interlaboratory variation in international normalized ratio determinations. *Am J Health Syst Pharm*. 2001; 58(8):684-688.

blood may be obtained, causing the operator to “milk” the finger causing a release of excess tissue factor, which prematurely activates the clotting process causing inaccurate INR results. Improper sample collection techniques and inherent sample matrix differences can result in INR values which are not comparable to a plasma-based test. Thus, validation studies designed exclusively for demonstrating equivalence between plasma-based devices and POC PT/INR devices may not be sufficient for complete validation of devices measuring whole blood.

The FDA is anticipating a robust discussion scientific and regulatory challenges associated with POC PT/INR devices at the upcoming public workshop at the White Oak Campus, Silver Spring, Maryland on January 25, 2016.

TOPICS FOR DISCUSSION

FDA is seeking input from the public on the following topics.

1. One source of error associated with POC PT/INR devices appears to be inadequate operator training or comprehension. FDA would like input on possible enhancements to existing operator training materials, or mechanisms to ensure demonstrated effective use of the POC PT/INR meters.
2. To decrease the numbers of device malfunctions, FDA is considering enhancing quality control requirements. Currently quality control includes electronic and internal quality control on the test strips. Potential external quality controls being considered are 1) contrived control materials and 2) demonstration of testing proficiency at defined intervals by utilizing paired testing of the device and a plasma-based lab test. What other type of quality control(s) enhancements could significantly improve device control and functioning?
3. CLSI document POCT14-A recognizes that results exceeding an INR of 5.0 generally have reduced trueness and precision in POC settings. In 510(k) applications submitted to FDA, the data above an INR of 5.0 are often collected from contrived specimens. FDA requests input on the usefulness for broad INR reportable ranges (e.g., 0.8 – 10 INR) in the setting of warfarin treatment monitoring and the feasibility of obtaining natural patient samples at the high INR range for device performance validation. FDA is considering whether manufacturers should validate the analytical measuring range with patient samples (not contrived).
4. INR results are used to monitor patients’ response to warfarin, yet some of the currently marketed POC PT/INR devices also report PT results. PT results reported from these devices are usually not the conventional prothrombin time in seconds and are typically calculated using complex mathematical algorithms. FDA requests input on the usefulness of these calculated PT results in the setting of warfarin treatment monitoring.

5. POC PT/INR devices have labeling that describes adjusting warfarin dose during home use of the device. FDA would like to discuss whether the appropriateness of a six-week stabilization window before prescription home use (patient self-testing) is an option. Are there cases where it would be appropriate to stabilize a patient with a POC PT/INR device versus a conventional plasma-based test? What special considerations should be assessed to enable POC PT/INR devices to be utilized to transition patients on and off of warfarin for medical procedures?
6. POC PT/INR devices on the market today employ a wide range of technologies for clot detection. The inherent differences between various clot detecting technologies may affect the comparability between the INR results obtained from different PT/INR devices. FDA is requesting input on whether additional technology-specific interference studies should be part of our evaluation for POC PT/INR devices. If so, what additional interferences should be assessed for both direct and indirect clot detection technologies?
7. What comparative devices should be used to evaluate the performance of a candidate POC PT/INR device in the method comparison study required for a premarket notification (510(k) submission). Please comment on the validation comparing a plasma-based laboratory method, a POC PT/INR predicate or both and what would be the clinically acceptable bias among the different INR ranges.